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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,683	MOSS ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 19-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment, filed 4/11/07, is acknowledged and has been entered. Claims 1-2, 7-8, 14-15, and 17-18 were amended. New claims 19-20 were added.

Objections/Rejections Withdrawn

2. The objection to the specification regarding the use of trademarks has been obviated by the amendments.

3. The objections to claims 7-8 and 14-15 have been obviated by the amendments.

Claim Objections

4. Claims 1-2 and 19-20 objected to because of the following informalities:

The claims recite methods "for assessment of possibility of cystic lung fibrosis". It appears that an article such as "the" is required before the word "possibility" in the claims.

5. Regarding claims 19-20, it is also noted that the claims refer to both "CAP 18" and "CAP-18" (hyphenated). Applicant is requested to employ consistent spelling of this protein throughout the claims.

Claim Rejections - 35 USC § 112

6. Claims 1-16 and 19-20 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter

7. Claims 1-2 as amended in the reply of 4/11/07 recite that the CAP18 "**specifically reacts with an antibody that specifically reacts with a protein having an amino acid sequence of SEQ ID NO: 1, 2, 3, or 4**".

Applicant's reply indicates that the amendments are supported by the disclosure at page 7, third full paragraph to the paragraph bridging pages 8-9 (Reply, page 9). However, support could not be found where indicated, for the following reasons.

The noted limitation refers to a property of the CAP 18 protein that is measured by the method. Specifically, the CAP 18 protein measured is being defined in the claim by reference to its ability to bind to antibodies, in particular those antibodies that specifically react with a protein having an amino acid sequence of SEQ ID NO:1, 2, 3, or 4.

However, the passages in the specification indicated do not describe such CAP 18 proteins having the claimed reactivity. Rather, pages 7-9 refer only to *antibodies* that may be used according to the instant invention. Thus, although the specification discloses the use of antibodies capable of binding to peptides having amino acid sequences of SEQ ID NO:1, 2, or 3 (see especially the paragraph bridging pages 8-9), it does not describe the genus of CAP 18 proteins that specifically react with such antibodies.

This distinction is significant because of the way that "CAP 18" is defined in the instant specification. Applicant has defined "CAP 18" so as to encompass "proteins having slight

structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc." (p. 7, the last full paragraph).

As such, although the property that the CAP 18 protein specifically reacts with antibodies that specifically react with SEQ ID NO:1-4-containing proteins might arguably be said to be an inherent characteristic of the full-length, native CAP 18 protein, there is nothing of record to indicate that proteins having structural differences from native CAP 18 would necessarily and always specifically react with such antibodies.

The attempt to define the genus of CAP 18 proteins being measured by the method by reference to a functional characteristic alone (the ability to react with an antibodies) fails to convey evidence of possession because Applicant has not disclosed what residues of CAP 18 are responsible for antibody binding, and therefore has not adequately described the relevant identifying characteristics of the genus.

Accordingly, the noted limitation represents a departure from the specification and claims as originally filed because it introduces a new subgenus of CAP 18 proteins that are defined by reference to their reactivity with a particular set of antibodies. This subgenus is not described in the specification.

8. In addition, the specification passages noted above refer to antibodies that bind to **peptides** having an amino acid sequence of **SEQ ID NO:1, 2, or 3**. By contrast, the claims recite antibodies that bind to **proteins** having the noted sequences. See also original claims 5, 7-8, 12, 14-15; and the specification at page 10, the third full paragraph; page 12, the second full paragraph; and page 18, the first full paragraph, which all refer to antibodies that bind to **peptides**. Since **peptides** and **proteins** differ in scope, the amendments represent a departure

from the specification and claims as originally filed because only antibodies that specifically bind to **peptides** of the noted sequences are disclosed. Given that it is well known in the art that antibodies raised against peptide fragments of a protein may not necessarily recognize the protein in the context of the full-length sequence, the noted limitation cannot be characterized as an inherent characteristic of the disclosed antibodies.

9. In addition, claims 1-2 as amended refer an antibody that "**specifically reacts**" with a protein having an amino acid sequence of SEQ ID NO:1, 2, 3, or 4. Although the specification mentions "specific binding" (see, e.g., page 18, the last paragraph), support could not be found for the limitation that the antibody "specifically reacts". The terms ***react*** and ***bind*** convey a different scope, since ***reaction*** of an antibody with a protein may also encompass reactions other than binding, such as proteolytic cleavage of the antibody by the protein. For these reasons, the disclosure of antibodies that ***specifically bind*** peptide antigens fails to convey evidence of possession of antibodies that ***specifically react*** with proteins as claimed.

Similarly, claims 1-2 also recite that the CAP 18 "**specifically reacts**" with the antibody; however, the specification only discloses "specific binding" among antibodies and antigens.

10. Finally, claims 1-2 as amended refer to an antibody that reacts with a protein having "an amino acid sequence of SEQ ID NO:1, 2, 3, **or 4**" (emphasis added). However, pages 7-9 only disclose antibodies capable of binding to peptides having amino acid sequences of SEQ ID NO:1, 2, or 3; there is no mention of SEQ ID NO:4. Rather, the only mention of SEQ ID NO:4 in the specification is at page 7, where this sequence is referred to as being the entire amino acid sequence of human CAP 18.

As such, the amendments to refer to antibodies that react with proteins having amino acid sequences of SEQ ID NO:4 represent new matter because such antibodies are not disclosed in the specification. Antibodies that specifically react with SEQ ID NO:4-containing proteins would also include antibodies that recognize epitopes present in regions of SEQ ID NO:4 other than SEQ ID NOs 1-3. Such antibodies are not described in the specification. Because of this difference in scope between the disclosed antibodies that bind to SEQ ID NOs 1-3-containing peptides and the claimed antibodies that bind to SEQ ID NOs 1-4, the amendments depart from the specification and claims as originally filed.

11. New claims 19-20 recite "CAP 18 having the amino acid sequence of SEQ ID NO:4". The specification refers to SEQ ID NO:4 at page 7, the third full paragraph, which discloses: "the entire amino acid sequence of human CAP 18 is appended hereto (SEQ ID NO: 4)".

Thus, the specification refers to SEQ ID NO:4 as the designation for the full-length human CAP 18 protein. However, the instant claims employ the term "**having**" in relation to SEQ ID NO:4. Because the specification does not specifically define the term "having" in the context of amino acid sequences, the claims may reasonably be interpreted as being open in scope. In other words, the claims may be construed as referring to CAP 18 proteins that include SEQ ID NO:4 but may also include additional amino acids. Such proteins are not described in the specification. The disclosure of the human CAP 18 *consisting of* SEQ ID NO:4 fails to convey evidence of possession of the genus of CAP 18 proteins that include SEQ ID NO:4 but which may also include other amino acids or components.

Written Description

12. Claims 1-16 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The elected invention is drawn to a method for the diagnosis of cystic fibrosis based by measuring the level of "CAP 18". Applicant has defined "CAP 18" so as to encompass "***proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.***" (p. 7, the last full paragraph, emphasis added).

As a result of this way in which "CAP 18" is defined according to the instant specification, the claims are drawn to methods of diagnosis based on the measurement of a large genus of proteins that differ structurally from native CAP 18, but which do not differ significantly in function. This genus would include, for example, proteins having deletions, additions, or substitutions to the native CAP 18 amino acid sequence (including fusion proteins), post-translational modifications, chemical modifications, etc. However, in describing only measurement of the native CAP 18 protein, the specification does not provide a written description to support evidence of possession of the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.".

As currently amended, the CAP 18 proteins measured are defined further in claims by reference to a functional characteristic, namely, the ability to react with an antibody that specifically binds with a protein "having an amino acid sequence of SEQ ID NO:1, 2, 3 or 4".

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

Although drawn to the DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co. The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or chemical name', of the claimed subject matter sufficient to distinguish it from other materials." Id. at 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin CDNA" or "mammalian insulin CDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAS might be described. "A description of a genus of cDNAS may be achieved by means of a recitation of a representative number of cDNAS, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." ld.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem. Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics; i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Although the inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.", per Lilly by structurally describing representative structural analogs or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

However, the instant specification does not describe the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc." in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses human CAP 18 (SEQ ID NO:4, see p. 7), it does not disclose what portions of this protein are responsible for function or behavior, and therefore does not disclose what "slight structural differences" would retain physiological function. The specification does not describe what types of structural differences would be encompassed, what structural features are shared among members of the genus, or provide detailed characteristics to identify the members of the genus. As such, one skilled in the art cannot readily envision the structure of the proteins to be measured. Furthermore, the specification does not provide any correlation between any common structure and function (i.e., "intravital function".

Similarly, the claims as amended require that the CAP 18 protein measured "specifically reacts with an antibody that specifically reacts with a protein having an amino acid sequence of SEQ ID NO: 1, 2, 3, or 4". This circular attempt to define the CAP 18 proteins that are measured based on their ability to be bound by an antibody fails to convey evidence of possession of the genus of CAP 18 proteins that may be measured, because the characteristics of the genus are not known.

Since the specification fails to adequately describe the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.", it also fails to adequately describe the method in which such proteins are measured and used in diagnosis of cystic fibrosis.

For example, the specification also discloses art-recognized methods for producing antibodies by immunizing animals with peptide portions of human CAP 18 (see p. 9-13). However, the specification fails to disclose any examples of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.", and fails to specifically identify what portions of this protein are responsible for binding to antibodies.

It is known in the art that minor changes to a protein sequence can abolish antibody binding (see enablement rejection below). Applicant has not disclosed what "slight structural differences" may be made without altering an antibody epitope, and has provided written description only for antibodies raised against the native human CAP 18 protein sequence. Applicant therefore has not described how to measure CAP 18 proteins that are structurally different from the native human CAP 18 protein sequence. One skilled in the art would not

envisage possession of the currently claimed methods of detection of the genus of variant CAP 18 proteins using antibodies raised against the native human CAP 18 sequence.

With respect to new claims 19-20, which recite that the CAP 18 protein is specified as one "having" the amino acid sequence of SEQ ID NO:4, it is noted that Applicant has not specifically defined the term "having" in the context of amino acid sequences (see also the new matter rejection above). Accordingly, the term may be construed as being open, such that the claims are drawn to methods of measuring CAP 18 proteins "having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.". As a result, the claims are drawn to methods of diagnosis by measuring a genus of CAP 18 proteins. So long as they include SEQ ID NO:4, many possible variants of SEQ ID NO:4 would be included in this genus, such as fusion proteins, proteins having additional amino acids on either end in addition to SEQ ID NO:4, and various post-translational and/or chemical modifications. Although in this case a partial structure (SEQ ID NO:4) has been provided, one skilled in the art cannot envisage possession of methods of *detecting* such variants given that even minor changes can abolish antibody binding.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

13. Claims 1-16 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed methods relate to the assessment of cystic fibrosis based on measurements of levels of "CAP 18". The application has been considered below with respect to the currently elected species of **diagnosis** of cystic fibrosis as the type of assessment.

The nature of the invention relates to the investigation of levels of human CAP 18 protein in bronchoalveolar lavage fluid (BALF) and expectoration samples in human subjects suffering from cystic fibrosis as compared to healthy human control subjects (see especially p. 27-28). The specification discloses measuring CAP 18 levels by use of antibodies raised against the human CAP 18 protein (SEQ ID NO:4; see p. 7 and p. 25, "Production of polyclonal antibody") and/or against partial peptide portions of the human CAP 18 protein, namely SEQ ID NO:1, 2, or 3 (see especially p. 9-10, 18 and 24-25).

However, as discussed above with respect to the written description requirement, Applicant has defined "CAP 18" so as to encompass "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc." (p. 7, the last full paragraph). Thus, the claims are not limited to detection of the native human CAP 18 protein (SEQ ID NO:4).

Although in new claims 19-20 the CAP 18 protein detected is specified as one "having" the amino acid sequence of SEQ ID NO:4, upon interpreting the claim language as being open, the claims are not limited to SEQ ID NO:4 but would also encompass diagnosis based on measurement of a genus of proteins, so long as they include SEQ ID NO:4.

As such, the claims are broadly drawn to methods of diagnosis based on the measurement of a genus of proteins that differ structurally from native CAP 18, but which do not differ significantly in function. This genus would include, for example, proteins having deletions, additions, or substitutions to the native CAP 18 amino acid sequence (including fusion proteins), post-translational modifications, chemical modifications, etc., as well as CAP 18 proteins from all species.

The specification does not provide sufficient enabling description of the claimed invention for the following reasons.

First, it is noted that the specification guides the skilled artisan to diagnose cystic fibrosis based on elevated levels of CAP 18 as compared to healthy controls (see especially p. 21). One skilled in the art would recognize that in order to be employed in diagnosis, a biomarker must be specific to the disease to be diagnosed. However, it is known that CAP 18 is elevated in various disease conditions that are unrelated to cystic fibrosis. For example, Applicant's own postfiling work teaches that CAP 18 is elevated in both cystic fibrosis as well as in COPD, and is elevated to comparable levels in both diseases (79.6 ± 93 vs. 75.3 ± 38.9 ng/ml, respectively) (Xiao et al., "Sputum Cathelicidin, Urokinase, Plasminogen Activation System Components, and Cytokines Discriminate Cystic Fibrosis, COPD, and Asthma Inflammation" (2005) *Chest* 128;2316-2326, in particular the abstract and p. 2319-2320, "CAP18 in Serum, BAL Fluid, and Sputum"). Applicant's work in copending application 2006/0057134 A1 (Kirikae et al.) also discloses that CAP 18 is markedly elevated in sputum in bacterial pneumonia patients as compared to controls, such that it can be used to diagnose this disease (see especially paragraphs 196-209, 238-242, and claims 25-32). In addition, Schaller-Bals et al. ("Increased Levels of Antimicrobial Peptides

in Tracheal Aspirates of Newborn Infants during Infection" *Am J. Respir Crit Care Med* **165** (2002), p. 992-995) teach that CAP 18 ("LL-37/hCAP-18") is elevated in infection and inflammation in newborns (see in particular the abstract).

These various references establish that CAP 18 is not a specific biomarker of cystic fibrosis, but rather is elevated in a number of distinct disease processes.

The instant specification fails to provide any guidance with regard to differential diagnosis—i.e., how cystic fibrosis may be diagnosed based on elevated CAP 18 levels alone, given that it is known that CAP 18 is elevated in a number of different diseases, and therefore is not specific to cystic fibrosis. Rather, all of the examples in the specification relate to subjects whose disease condition was already known, i.e., those subjects who were already diagnosed with the disease. As a result, one skilled in the art would not know, upon obtaining a finding of elevated CAP 18 levels in a subject, whether to diagnose a subject with cystic fibrosis, COPD, bacterial pneumonia, or infection and inflammation.

Furthermore, in describing only measurement of the native human CAP 18 protein, the specification does not enable one skilled in the art to detect the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.". The specification discloses only the human CAP 18 protein with the amino acid sequence of SEQ ID NO:4, as well as the partial peptides thereof SEQ ID NO:1-3. However, the claims are open-ended given the definition of "CAP 18" in the specification; it expands the detected "CAP 18" proteins so to include additions, truncations, substitutions, as well as other types of modifications to the sequence shown in SEQ ID NO:4.

The prior art teaches that antibodies raised against the native CAP 18 protein would not reasonably be expected to be reactive with "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.". For example, Lederman et al. (Molecular Immunology (1991) 28: 1171-1181, see entire document) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody. Further, Li et al. (PNAS 1980. 77: 3211-3214, see entire document) in the context of constructing analogs, disclose that immunoreactivity is dissociated from other biological activities. Similarly, Colman et al. (Research in Immunology, 1994; 145(1): 33-36) teach that single amino acid changes in an antigen can effectively abolish antibody antigen binding (see entire document, particularly page 34). Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444) also teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding (see entire document, particularly Results on pages 435-436).

The specification discloses that "CAP 18" may be detected through use of an antibody capable of specific binding to CAP 18 (p. 8). However, in describing only antibodies raised against the known sequence of native human CAP 18, the specification does not provide a sufficient enabling description of an antibody reactive towards the genus of "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc.". Therefore, the specification does not teach the skilled artisan how to predictably measure "proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc." or to employ such measurements for diagnosis, given that antibodies

raised against the native CAP 18 protein would not reasonably be expected to bind to such structural analogs.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling." Given that it is apparently not even known whether CAP 18 even exists and is present in all mammalian species, the specification fails to teach the skilled artisan how to detect CAP 18 in all mammals and carry out diagnosis of cystic fibrosis therefrom.

The claims are also broad with respect to the type of biological sample, as the specification indicates that any type of biological sample may be employed, e.g. any type of excretion (see p. 6). However, the data presented for BALF and expectoration samples do not reasonably correlate with this claim scope. Applicant's own postfiling work teaches that serum levels of CAP 18 were similar in subjects with cystic fibrosis as compared to healthy controls (see Xiao et al., especially p. 2319, right column, the last paragraph, and p. 2324, right column, the last paragraph). In this light, it is clear that the specification does not teach how to employ all types of samples to diagnose cystic fibrosis based on levels of CAP 18, given that serum CAP 18 levels are no different in healthy vs. disease populations and therefore could not be successfully used in the claimed methods.

In summary, it is known that CAP 18 is not a specific marker of cystic fibrosis, but rather is elevated in various unrelated conditions, yet the specification does not provide guidance in regard to differential diagnosis, and therefore fails to teach the skilled artisan how to predictably diagnose cystic fibrosis based on CAP 18 levels. The prior art also establishes that CAP 18 proteins differ significantly in amino acid sequence among different species, and further that minor changes to a protein sequence can abolish antibody binding, which speaks to the unpredictability in using antibodies raised against one protein sequence to detect a distinct protein. Taken together with the lack of direction/guidance presented in the specification regarding detection of all CAP 18 proteins or structural analogs thereof and in all sample types (as well as the diagnosis of cystic fibrosis thereby), and the lack of working examples directed to same, and the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

14. Claims 1-16 and 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Independent claims 1 and 2 recite measuring the level of "CAP 18", which is indefinite because the specification defines "CAP 18" so as to encompass **"proteins having slight structural differences from native (non-mutated) CAP 18 but exhibiting no significant differences in terms of intravital function, behavior, etc."** (p. 7, the last full paragraph).

However, it is noted that the above definition of "CAP 18" is open-ended, i.e. not limiting, and the specification does not provide a standard for ascertaining the scope of the claim since. The claims are clearly not limited to detection of native CAP 18; however, the specification does not define or clearly exemplify what proteins would be encompassed by this definition. It is not clear what types of structural differences or modifications, and also what *extent* of modification, would be encompassed by the claim. For example, would proteins differing by 1 or 10 amino acids from the native CAP 18 protein be considered to be "slightly different"? Homologs from other species? The specification does not define or provide a standard for understanding what would be considered to be a "slight structural difference". Because of this way that "CAP 18" is currently defined in the instant specification, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Furthermore, the use of the designation "CAP 18" alone to describe a particular protein renders the claim indefinite because different laboratories may use the same laboratory designation to define completely distinct proteins or protein fragments. This is true in the case of

"CAP 18": the specification states that the entire amino acid sequence of human CAP 18 is given as SEQ ID NO:4 (see p. 7), which is a 170-amino acid protein. However, Montelaro et al. (US 6,835,713 B2) describe human CAP 18 (hCAP18) as being a 37-amino acid peptide (see column 1, lines 57-61). By contrast, Applicant's postfiling work (Xiao et al., discussed above) identifies human CAP18 as an 140-amino acid protein (see p. 2317, left column, the first paragraph). As such, it is not clear what protein sequence is being detected since the claim refers only to "CAP 18" but does not adequately identify the species to be detected. Amendment of the claims to recite the SEQ ID NO may obviate this aspect of the rejection.

For all of the above reasons, the metes and bounds of the claims cannot be determined.

16. Similarly, new claims 19-20 refer to "CAP 18 having the amino acid sequence of SEQ ID NO:4". Although in this case reference is made to a particular sequence, because of the use of the transitional phrase "having", the claim may reasonably be interpreted as open in scope (see also the rejection under 112, 1st paragraph above). In other words, the claim may be construed as referring to CAP 18 proteins that include SEQ ID NO:4 but may also include additional amino acids. Such an open-ended scope, when coupled with the way in which "CAP 18" is defined in the specification, raises many of the same issues noted above. It is unclear which proteins would fall within the scope of the claim since proteins with "slight structural differences" are encompassed but the specification does not define, clearly exemplify, or otherwise provide a standard for determining whether a given structurally different protein would be encompassed by the claim or not.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-7 and 10-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Bals et al. ("Salt-Independent Abnormality of Antimicrobial Activity in Cystic Fibrosis Airway Surface Fluid" *Am. J. Respir. Cell Mol. Biol.* **25** (2001), p. 21-25) and in light of the evidence of iHOP (Information Hyperlinked over Proteins – data for CAMP, cathelicidin antimicrobial peptide, p. 1, downloaded from http://www.ihop-net.org/UniPub/iHOP/gs/86912.html on 01/04/2007) and Larrick et al. ("Human CAP18: a Novel Antimicrobial Lipopolysaccharide-Binding Protein" *Infection and Immunity* 63 91995), 1291-1297)

Bals et al. teach measuring the level of CAP 18 ("LL-37/hCAP-18") in a biological sample from humans (bronchoalveolar lavage fluid and human bronchial xenografts generated from respiratory epithelial cells of children) and correlating the measurement with cystic fibrosis (see the entire document, in particular the abstract; p. 21, right column; p. 22, left column; Figures 3-4; and p. 23-24, "Concentrations of Known Antimicrobial Peptides Are Equivalent in CF and Normal ASF").

Bals et al. compared CAP 18 levels in cystic fibrosis and healthy control subjects (Figures 3-4), which reads on the claimed correlation step as recited in claims 1-2 for the following reasons. Although Bals et al. note that the difference was not statistically significant, it is apparent in Figure 4 in particular that there were nonetheless differences between control and

cystic fibrosis samples. Specifically, Figures 4A and 4B depict increased concentrations of LL-37/hCAP-18 in the cystic fibrosis group (hatched lines) as compared to the control group (shaded boxes without hatched lines). Thus, despite the fact that Bals et al. conclude that the difference was not significant, since an increase was in fact observed the reference is anticipatory.

With respect to the recitation of a method for assessment of "possibility" of cystic lung fibrosis, it is noted that such a recitation was not found to further limit the method defined by the claims. In particular, the statements in the preamble do not provide antecedent basis for terms in the body of the claim and are not essential to understand the limitations or terms in the claim body. In addition, the preamble recites the purpose or intended use of the claimed invention. Such statements merely define the context in which the invention operates and usually will not limit the scope of the claim (MPEP 2111.02 and DeGeorge v. Bernier, Fed. Cir. 1985, 226 USPQ 758, 761 n.3).

Furthermore, given the breadth of assessment of "possibility" of cystic fibrosis (as exemplified by the various types of assessment that would be encompassed by this term as recited in claim 9), the methods of Bals et al. in which cystic fibrosis was assessed in terms of LL-37/hCAP-18 levels read on the claims since increases in the levels of this protein were observed relative to controls, as depicted in Figure 4. Put another way, Bals et al. assessed the possibility that cystic fibrosis is associated with altered LL-17/hCAP-18 levels, which reads on the claimed invention in the absence of a specific definition of "assessment of possibility of cystic lung fibrosis".

The protein detected by Bals et al. (LL-37/hCAP-18) anticipates the claim limitation of being "CAP 18" in light of the evidence of iHOP, which teaches that hCAP-18, CAP-18, and LL37 are synonyms that designate the same protein (p. 1, top right).

This protein also specifically reacts with an antibody that specifically binds with a protein having an amino acid sequence of SEQ ID NO:1-4 as claimed, since Bals et al. teach polyclonal antibodies raised against the C-terminal 37 amino acids of LL-37/hCAP-18 (see page 1291, "Preparation of Antibodies..." and p. 22, left column, "Determination of Peptide Concentrations..."). As can be seen in the instant sequence listing for the entire amino acid sequence of CAP 18 provided by Applicant as SEQ ID NO:4, SEQ ID NOs 1-3 are all included in the last 37 residues of the protein (see the sequence listing filed 9/20/04). Given that the polyclonal antisera of Bals et al. did indeed bind to the LL-37/hCAP-18 protein (see Figure 3), it is apparent that the antisera react with proteins having SEQ ID NOs 1-3. See also Larrick et al. at Figure 2. Likewise, the LL-37/hCAP-18 protein detected by Bals et al. specifically bound to the antisera.

With respect to claims 4, and 11, the measurement of CAP18 was via antigen-antibody reaction using polyclonal antisera (se p. 21, right column, "Preparation of Antibodies..." and p. 22, left column, "Determination of Peptide Concentrations...").

With respect to claims 5 and 12, the antibody of Bals et al. was raised against LL-37/hCAP-18 containing the C-terminal 37 amino acids (see p. 21, right column, "Preparation of Antibodies..."). Larrick et al. provide evidence that this peptide has "an amino acid sequence of SEQ ID NO:1" as claimed, in that (for example) it includes the amino acid sequence "Lys—Glu" at position 115-116 (see Figure 2, the sequence provided for "Human"). As such, the antibody of

Bals et al. meets the limitation of being capable of binding to a peptide having an amino acid sequence of SEQ ID NO:1 because as reflected by Applicant's sequence listing, SEQ ID NO:1 also includes the "Lys—Glu sequence at positions 5-6 and also 10-11 (see the sequence listing filed 9/20/04).

With respect to claims 6-7 and 13-14, Bals et al. teach bringing the sample into contact with a solid phase (nitrocellulose membrane) so as to immobilize the CAP 18, adding the polyclonal antibody specific for CAP 18 to form a complex, and detecting the complex using a secondary peroxidase-labeled antibody (p. 22, left column, "Determination of Peptide Concentration..." and Figure 4).

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 8 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bals et al. in light of iHOP and Larrick, and in view of Weinberg et al. (US 6,187,536 B1).

Bals et al. is as discussed above, which teaches methods for measuring CAP 18 by dot-blot and immunoblot assay. However, the reference fails to specifically teach measuring CAP 18 using a sandwich-type, two-antibody immunoassay as recited.

However, such immunoassay formats were well known in the art at the time of the invention; for example, Weinberg et al. teach immunoassays comprising the steps of bringing into contact a solid phase support in which a first anti-protein antibody is immobilized with a test sample to form a complex or "sandwich" (see column 21, line 44 to column 22, line 7). Subsequently, the complex is detected either via a detectable second antibody or a third detectable antibody. Weinberg et al. teach that in contrast with simple immunoassays such as dot blot or Western blot, "two-site" or "sandwich" assays as detailed above provide excellent results and can be made quantitative.

Therefore, it would have been obvious to one of ordinary skill in the art to employ the sandwich immunoassay format taught by Weinberg et al., using two CAP 18-specific antibodies, in order to measure CAP 18 in the method of Bals et al. because Weinberg et al. teach that such immunoassays provide excellent results as compared with simple dot blot or Western blot assays, which are the methods used in Bals et al.

Response to Arguments

22. Applicant's arguments filed 4/11/07 have been fully considered.

23. With respect to the rejections of claims 1-16 under 35 USC 112, 1st paragraph (written description), Applicant has not specifically argued the grounds of rejection but states that the amendments to claims 1-2 and the addition of new claims 19-20 have overcome the rejection (see Reply, pages 10-11), to which the Examiner disagrees for the reasons noted above in the rejection.

24. With respect to the rejections of claims 1-16 under 35 USC 112, 1st paragraph (enablement), it is noted that Applicant's amendments to recite assessment in *humans* has obviated one of the grounds of rejection. However, with respect to the remaining grounds of rejection, Applicant's arguments (see pages 11-12) were fully considered but not found persuasive.

Applicant argues (see page 12) that the claims have been amended to recite that the method is for the "assessment of the possibility of cystic fibrosis". However, the amendments to refer to the "possibility" of cystic fibrosis do not specifically address the grounds on which the rejection was made. It is maintained for reasons of record that the teachings in the specification do not enable the skilled artisan to diagnose cystic fibrosis as claimed, in particular given that CAP 18 is known in the art to be elevated in a number of different diseases (see above and the previous Office action at pages 12-13).

With respect to the grounds of rejection as to the type of biological sample (see above and the previous Office action at page 16, the second paragraph), Applicant's reply does not include arguments traversing this aspect of the rejection.

25. With respect to the rejections of claims 1-7 and 10-14 under 35 USC 102(b) as being anticipated by Bals et al., Applicant's arguments (see pages 13-14) have been fully considered

but are not persuasive of error. Applicant argues that because Bals et al. concluded that the levels of CAP-18 were not significantly different between CF and controls, that Bals et al. teaches away from the invention (Reply, the paragraph bridging pages 13-14). However, arguments that the alleged anticipatory prior art teaches away from the invention are not germane to a rejection under section 102. See MPEP 2131.04. Furthermore, the rejected claims do not recite methods for diagnosis of cystic fibrosis, but rather "assessment of possibility of cystic lung fibrosis". Given such broad terminology, the reference is anticipatory for the reasons detailed above.

26. With respect to the rejections of claims 8 and 15 under 35 USC 103(a) as being unpatentable over Bals et al. in view of Weinberg et al., Applicant does not separately argue the limitations of the dependent claim but argues as above that Bals et al. teaches away from the present invention because it teaches that levels of LL37/CAP 18 were not significantly different between cystic fibrosis and controls (Reply, pages 13-14). Although the Examiner would agree this conclusion by Bals et al. teaches away from *diagnosis* of cystic fibrosis based on measurement of CAP 18, the rejected claims recite only "assessment of possibility of cystic lung fibrosis", which would include methods of investigating whether LL37/CAP 18 levels are altered in cystic fibrosis, as in Bals et al. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Given that sandwich immunoassays were well known in the art, it is maintained it would have been obvious to employ such methods for performing the methods of Bals et al.

Conclusion

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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